SYNTHETIC ANALOGS AND HOMOLOGS OF TETRAHYDROCANNABINOL

BY

CARL MAYN SMITH

B. S., University of California, 1936

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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INTRODUCTION

The work of Adams and his students[1] on the structure of cannabidiol, the second pure compound to be isolated from hemp extracts, showed Cahn's[2] structure for cannabinol to be incorrect; and led to the synthesis of this latter compound, showing it to be 1-hydroxy-3-n-amyl-6,6,9-trimethyl-6-dibenzopyran. In the course of the synthesis of cannabinol by a different method[3], 7,8,9,10-tetrahydrocannabinol was obtained; this compound had a high marihuana potency. Also it was discovered that the marihuana inactive cannabidiol could be isomerized by acidic reagents to tetrahydrocannabinols of high potency. These results have necessitated a critical survey of available pharmacological tests. The purpose of this thesis has been to accomplish this survey and to discuss the preparation and the potencies of some additional analogs and homologs of tetrahydrocannabinol.

DISCUSSION

Of the three tests available, the Geyer rabbit test[4], the mouse-sheep prolongation test[5], and the dog-ataxia test[6] only the latter is capable of yielding results which follow clinical findings closely; and with this last test a careful application of the Principle of Bioassay by Approximation[7] is necessary to aid in eliminating the large inner and intra-individual variations so characteristic of the effects of hemp preparations on humans and animals.

The first synthetic work attempted was to prepare an isomer of synthetic tetrahydrocannabinol, with the alicyclic double bond unconjugated with the aromatic ring, by condensation of properly substituted carbethoxycyclohexane-1,3-diones with olivetol followed by suitable transformations on the keto-tetrahydro-6-dibenzopyrones which might be so obtained. This line was abandoned when it was found that definite products could not be isolated in a test condensation between 4-carbethoxy-5-methyleyclohexanedione-1,3 and orcinol.

Tetrahydrocannabinol analogs in which the 9-methyl group was lacking, wherein the 9-methyl group was shifted to the 8-and to the 10- positions, and wherein the 6-methyl groups were replaced by two ethyl and by two n-propyl groups were next prepared in a manner entirely analogous to that in which synthetic tetrahydrocannabinol was prepared; namely, by condensing the appropriate carbethoxycyclohexanones with olivetol and by subsequent treatment with suitable Grignard reagents of the tetrahydro-6-dibenzopyrones thus obtained. These compounds were uniformly less active than the parent compound.

Condensation of pulegone with olivetol, using phosphorous oxychloride as condensing agent, yielded an optically active resin, the properties of which corresponded quite closely to those of synthetic tetrahydrocannabinol. However the potency of this material was only 0.58 compared to synthetic tetrahydrocannabinol as a standard.

Since the series of 1-hydroxy-3-n-alkyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans n-propyl through n-octyl had been prepared in this laboratory[8] and had shown interesting variations in marihuana potency, it was decided to prepare the corresponding series of hexahydrodibenzopyrans by reduction of the above, the series n-propyl through n-octyl of 5-n-alkylresorcinol pulegone condensation products, and finally the series of dihydro-reduction products of these latter substances. The reduction of the majority of the tetrahydrocannabinol homologs and of the pulegone-5-n-alkyresorcinol condensation products was carried out with Raney nickel in absolute alcohol at 500 to 700 pounds pressure and 100° C., since it was found that these substances varied widely in ease of reduction when platium oxide catalyst in glacial acetic acid was used.

The marihuana potencies of the hexahydrocannabinol homologs were uniformly less than the corresponding tetrahydro compounds, and exhibit a maximum at the compound with the 3-hexyl group just as do the tetrahydro compounds.

The pulegone-5-n-alkylresorcinol products however, exhibit a potency maximum at the n-octylresorcinol compound and are of higher potency for the n-heptyl and the n-octyl

members than are the corresponding, unequivocal tetrahydrocannabinol homologs. The dihydro-pulegone-5-n-alkylresorcinol products are uniformly less active than the original substances, but they exhibit a displacement of maximum potency to the n-heptyl derivative.

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ADDENDUM

AN ATTEMPT TO PREPARE 4-AMINO-2,2′-DIBROMO-4′-DINITROBIPHENYL

INTRODUCTION AND THEORETICAL

Calvin[1] has suggested that the fact that 2,2′-dibromo-4,4′dicarboxydiphenyl is resolvable and that 2,2′-dibromo-4,4′-diaminobiphenyl is not can be explained if an ionic quinoid resonance state can exist or contribute to the structure of the first compound and not in the second. For the transfer of an electron necessary to produce the ionic resonance state one group in the para position must be an electron donor and the other an electron acceptor. The carbonyl group satisfies both of these requirements, but the amino group can act only as an electron donor. Hence in the dicarboxy compound the ionic quinoid state contributes to the resonance ensembled of the whole molecule effectively shortening the ring to ring bond and causing sufficient interaction of the ortho groups to enable the compound to be resolved. On this basis Calvin has predicted that 4-amino-2,2′-dibromo-4′-nitrobiphenyl should be resolvable, since the nitro group is capable of acting as an electron acceptor. It was the purpose of this work to prepare and attempt to resolve this compound.

EXPERIMENTAL

A plan to obtain the desired compound involving an Ullman reaction on 2-bromo-4-nitroiodobenzene to give 2,2′-dibromo-4,4′-dinitrobiphenyl had to be abandoned, because no crystalline products could be obtained from the Ullman reaction.

The above dibromodinitrobiphenyl was obtained by replacement of the amino groups in 2,2′-dibromobenzidine with nitro groups through the tetrazonium difluoroborate by the Organic Synthesis procedure[2]. Attempts to reduce 2,2′-dibromo-4,4′-dinitrobiphenyl by the sodium polysulfide method[3] gave only dibromo benzidine. This fact was not immediately recognized, and an attempt was made to resolve this compound through its d-camphor sulfonate. This salt mutaro-

tated in menthanol solution from a positive value to an approximately equal negative rotation. This behavior was very probably due to the establishment of a salt, ketimine equilibrium[4].

The amine obtained from the salt was inactive; this is in agreement with the work of Adams and Searle.

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VITA

The writer was born April 23, 1914, near Martinsdale, Montana. However, all of his primary and secondary education was obtained in the public schools of Long Beach, California. He attended California Institute of Technology during the academic years of 1932-1934. From 1934 to 1936 he attended the University of California at Berkeley, where he was graduated in December, 1936, with a Bachelor of Science Degree. During the past four years he has pursued graduate work at the University of Illinois.